#11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TERM EXTENSION

In re Patent of	:	Weyer et al.
Patent No.	:	4,379,785
Issued	:	April 12, 1983
For	:	Heterocyclic Substituted Sulfonyl Ureas, and their Use

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC §156

January 19, 1996

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

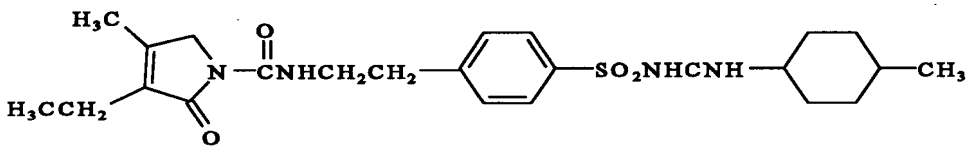
Attention: Box Patent Term Extension

Sir:

Applicant Hoechst Atiengesellschaft, a German corporation, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,379,785, granted to Rudi Weyer, Volker Hitzel, Karl Geisen and Günter Regitz. Applicant hereby submits this application for extension of patent term under 35 USC § 156, by providing the following information as required by 37 CFR §1.740.

(1) **A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT:**

The generic name of the approved product is glimepiride. Its chemical name is 1-[[p-2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(4-methylcyclohexyl)urea. It has the following structure:



Its molecular formula is $C_{24}H_{34}N_4O_5S$ and its molecular weight is 490.62.

(2) **COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH THE REGULATORY REVIEW OCCURRED:**

The regulatory review of the approved product occurred under Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 USC § 355.

(3) **IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE.**

Glimepiride was approved by the FDA for commercial marketing pursuant to Section 505 of FFDCA (21 USC § 355) on November 30, 1995.

(4) **IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FEDERAL FOOD, DRUG AND COSMETIC ACT.**

The sole active ingredient of the approved new drug is glimepiride as identified above under paragraph 1. It has not previously been approved by FDA for commercial marketing or use under FFDCA.

(5) **STATEMENT THAT THIS APPLICATION FOR PATENT TERM EXTENSION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED AND IDENTIFICATION OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.**

This application is to be hand-delivered to the United States Patent and Trademark Office on January 22, 1996 which is within the sixty day period starting from November 30, 1995 and ending on January 29, 1996, permitted for submission pursuant to 37 C.F.R. § 1.720(f).

(6) **COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT.**

A complete identification of the patent is presented as follows:

Names of the Inventors:	Rudi Weyer Volker Hitzel Karl Geisen Günter Regitz
Patent Number:	4,379,785
Filing Date:	December 17, 1980
Issue Date:	April 12, 1983

Date of Original Expiration: April 12, 2000

Date of Expiration under: the Uruguay Round Agreements Act, P.L. 103-465 ("URAA") December 17, 2000

Assignee: Hoechst Aktiengesellschaft

(7) **COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT.**

A copy of said U.S. Patent Serial No. 4,379,785 is attached hereto as Exhibit A.

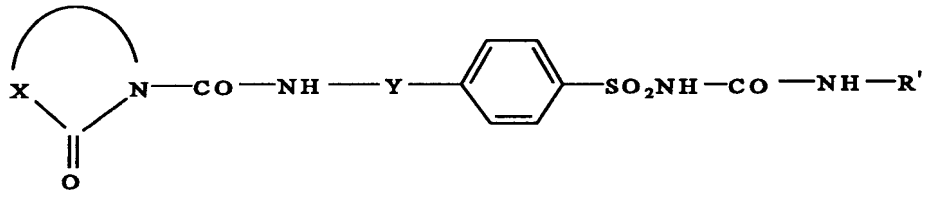
(8) **COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OR MAINTENANCE FEE PAYMENT OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT.**

The patent application which matured into U.S. Patent No. 4,379,785 was filed in the United States Patent and Trademark Office on December 17, 1980. The required three maintenance fees have been duly paid. Copies of "Maintenance Fee Transmittal Form (PTO-1536) for the eight and twelve year payments are submitted herewith as Exhibits B-1 and B-2. A copy of the response to a Public Inquiry indicates payment of the four year extension (Exhibit B-3).

No statutory disclaimer certificate of correction or re-examination certificate has been issued.

(9) **STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIM READS ON THE APPROVED PRODUCT OR METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT.**

Claim 1 of the '785 patent claims a sulfonyl urea compound of the formula



Claim 1 reads on glimepiride when X is alkenylene having 3 carbon atoms substituted by 2 alkyl groups, one having 1 carbon atom and the other having 2 carbon atoms; Y is alkylene having two carbon atoms and R^1 is cycloalkylalkyl.

Claim 3 reads directly on glimepiride.

Claim 5 claims a pharmaceutical composition for lowering the blood sugar level which comprises a hypoglycemically effective amount of a sulfonyl urea or salt thereof as defined in Claim 1 and a pharmaceutically acceptable carrier therefor. Claim 5 reads on the approved product when X is alkenylene having three carbon atoms substituted by two alkyl groups, one having 1 carbon atom, the other having two carbon atoms; Y is alkylene having two carbon atoms and R^1 is cycloalkylalkyl in the formula of Claim 1.

Claim 6 claims a method for lowering the blood sugar level in a patient suffering from diabetes which comprises orally administering a hypoglycemically effective amount of a sulfonyl urea or salt thereof as claimed in Claim 1. Claim 6 reads on a method for lowering the blood sugar level in a patient when administering the approved drug when X is alkenylene having three carbon atoms substituted by two alkyl groups, one having 1 carbon atom, the other having two carbon atoms; Y is alkylene having two carbon atoms and R^1 is cycloalkylalkyl in the formula of Claim 1.

(10) **STATEMENT OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 USC §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD.**

The Effective Date of the IND application: (30 days after the date of receipt by FDA)	July 28, 1988
The IND number:	IND 31,759
The Date on which the NDA was initially submitted (date of receipt by FDA):	August 30, 1994
The NDA number:	NDA 20-496
The Date on which the NDA was approved:	November 30, 1995

(11) **BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT.**

Hoechst-Roussel Pharmaceuticals Incorporated (HRPI) was an affiliate of Hoechst A.G. (Applicant) and was licensed by the latter to market the approved product in the United States. On January 1, 1996 HRPI became part of Hoechst Marion Roussel, a wholly owned affiliate of Hoechst A.G., as a result of a merger. A copy of merger document is attached as Exhibit C. The appropriate steps are being taken with the FDA to reflect the merger. HRPI submitted an IND on June 23, 1988 (which became effective on July 28, 1988) and subsequently submitted an NDA which was received by the FDA on August 30, 1994 and obtained approval from the FDA of the NDA on November 30, 1995. The then marketing applicant (HRPI) believed that it pursued its activities with due diligence throughout the regulatory review period, namely the testing phase and the approval phase. Significant activities undertaken by HRPI during the regulatory review period are briefly described in EXHIBITS D-1 and D-2. The former exhibit relates to the testing phase, whereas the latter exhibit relates to the approval phase.

(12) **STATEMENT THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:**

Applicant believes that the subject patent is eligible for patent term extension pursuant to 35 USC 156(a) for the following reasons:

(1) The term of the subject patent has not expired before this application is being submitted for its extension.

(2) The term of the subject patent has never been extended.

(3) This application for patent term extension is submitted by an authorized agent of the owner of record (Hoechst A.G.) of the subject patent.

(4) The product has been subject to a regulatory review period before its commercial marketing or use as evident from Paragraph 11 above.

(5) The permission for the commercial marketing or use of the product after the regulatory period is the first permitted commercial marketing or use of the product under the provisions of FFDCA (21 U.S.C. § 355).

Applicant believes that the subject patent is entitled to 1569 days of term extension. This length of extension has been calculated as follows: Details of the key days are presented in Exhibits D-1 and D-2 and calculation forms in Exhibits D-3 and D-4.

(1) Number of days of the testing phase which is subsequent to the patent issue date is 2224 days (Between 7/28/88 and 8/30/1994).

(2) Number of days for the approval phase subsequent to the patent issue date is : 457 days (between 8/30/1994 and 11/30/1995).

The sponsor of the IND and DNA for the subject approved product (Hoechst-Roussel Pharmaceuticals Incorporated, licensee of Hoechst A.G.) acted with due diligence throughout the testing and the approval phases as is evident from the Exhibits D-1 and D-2.

(3) One half of the testing period (subsequent to the subject patent issue date and supported by due diligence) is 1112 days:

(4) The sum of the period recited under the preceding paragraph (3) and the period recited preceding under paragraph (2) is 1569 days (modified regulatory review period);

(5) The subject patent issued prior to September 24, 1984 (Effective Date of the 1984 Waxman - Hatch Act, including 35 USC § 156).

(6) The date of approval of the NDA for the subject approved product is November 30, 1995.

(7) The original expiration date of the subject patent is April 12, 2000;

(8) Adding the modified regulatory review period of 1569 days onto the original expiration date gives an expiration date of July 19, 2004.

(9) The extension period is subject to the five (5) year limitation under 35 USC § 156(g)(6)(B) because (i) the patent was issued before the Effective Date of 35 USC § 156 (Waxman-Hatch Act); and (ii) the filing of the IND occurred after the Effective Date of 35 USC § 156. Thus, the maximum five-year period for subject patent, if applicable, is to April 12, 2005.

(10) The patent term extension is also subject, under 35 USC §156(c)(3), to the fourteen (14) year limitation as to the net effective life of the patent after the NDA approval. This limitation dictates that the subject patent cannot be extended beyond November 30, 2009.

(11) In light of the conclusion stated under the preceding paragraphs (8), (9) and (10), the controlling limitation is the 1569 day extension recited in preceding paragraph (8). Thus, the extended expiration date of the subject

patent is believed to be July 19, 2004 without consideration of URAA (Exhibit D-3).

(12) Under the provisions of the URAA which took effect June 8, 1995, the subject patent is entitled to a term of the longer of (a) 20 years from the original effective U.S. filing date or (b) 17 years from the date of issue.

(13) Since the application which matured into the subject patent was filed on December 17, 1980, the URAA term for the subject patent is 20 years and the expiration date is December 17, 2000. Accordingly, applicant believes that it is entitled to an extension of 1569 days to the URAA term of the subject patent which would extend its expiration date to April 4, 2005 (Exhibit D-4).

13. **STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE MATERIAL INFORMATION**

The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services under 37 CFR 1.765 any information which is material to the determination of entitlement to the extension sought herein.

HRPI, the marketing applicant which received the NDA approval on November 30, 1995, became part of Hoechst Marion Roussel Incorporated ("HRPI") on January 1, 996 as a result of a merger. It is anticipated that HMRI will market the approved product. The appropriate steps are being taken at the FDA to effect a name change. However, since HMRI is also an affiliate of the instant applicant, Hoechst A.G., the merger is not believed to affect the instant application for patent term extension.

14. **THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION**

Please charge the **Deposit Account Number** 08-2445 in the amount of $1,060.00 as the fee covering the instant application for patent term extension. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 08-2445.

15. **THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED**

Please forward all inquiries and correspondence relating to this application for patent term extension to:

Barbara V. Maurer, Esq.
Patent Department
Hoechst Celanese Corporation
Route #202-206
P.O. Box 2500
Somerville, New Jersey 08876-1258
Telephone #: (908) 231-4079.

16. **A DUPLICATE OF THE APPLICATION PAPERS, CERTIFIED AS SUCH**

A duplicate of this application papers is enclosed herewith. The undersigned attorney hereby certifies that said duplicate is a true copy of the original set of application papers.

17. **DECLARATION OF ATTORNEY:**

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that by virtue of the enclosed POWER OF ATTORNEY (Exhibit E) duly signed by authorized representatives of Hoechst Atiengesellschaft, Federal Republic of

Germany, (the owner of record of the subject patent), I am the authorized agent designated by Hoechst A.G. for the purpose of submitting this application for patent term extension, and hence, have the general authority to submit and prosecute this application on behalf of Hoechst A.G.; that I have reviewed and understand the contents of this application being submitted; that I believe the subject patent (U.S. Patent No. 4,379,785) is eligible for extension pursuant to 37 CFR § 1.710; that I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR §1.720.

Respectfully Submitted,

Barbara V. Maurer

Barbara V. Maurer
(Reg. No. 31,278)
Attorney for Applicant(s)
Hoechst-Roussel Pharmaceuticals Inc.
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Somerville, New Jersey 08876-1258
Telephone#: (908) 231-4079

EXHIBIT E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: Application for Extending the Term of Weyer et al., U.S. Patent 4,379,785

POWER OF ATTORNEY

WHEREAS, Hoechst Aktiengesellschaft (hereinafter "Hoechst") having its principal place of business at 6230 Frankfurt am Main 80, Federal Republic of Germany, is the lawful sole assignee of Weyer et al., U.S. Patent 4,379,785 issued on April 12, 1983, which covers a compound known generically as glimepiride.

WHEREAS, Hoechst and its affiliate, Hoechst-Roussel Pharmaceuticals Incorporated (hereafter "HRPI"), are desirous of marketing in the United States pharmaceutical products containing glimepiride as an active ingredient;

WHEREAS, on November 30, 1995 the United States Food and Drug Administration (FDA) approved HRPI's New Drug Application to market glimepiride in the United States;

WHEREAS, 35 U.S.C. Section 156(a)(3), provides that an application for extension of a patent term can be submitted by the owner of record of the patent or its agent; and

WHEREAS, Hoechst and HRPI are desirous of filing an application for extending the term of said Weyer et al., '785 patent;

NOW, THEREFORE, Hoechst hereby designates, Barbara V. Maurer (Reg. No. 31,278); Jerome Rosenstock (Reg. No. 25,456); Raymond R. Wittekind (Reg. No. 27,413) and Kenneth A. Genoni (Reg. No. 21,192). who are employees of Hoechst Celanese Corporation and serve HRPI in intellectual property matters, as agents for submitting and prosecuting the application for extending the term of said '334 patent, and respectfully requests the Commissioner to recognize them as authorized agents of Hoechst and HRPI for the purpose stated above.

HOECHST AKTIENGESELLSCHAFT

By: ppa Burgelhardt i.V. Lutz

Title: Prokurist Authorized Signatory

Date: January 3, 1996

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

EXHIBIT B-1

PAYOR NUMBER
000149

HOECHST AKTIENGESELLSCHAFT
CENTRAL PATENT DEPARTMENT
P. O. BOX 800320
D-6230 FRANKFURT AM MAIN 80
FEDERAL REPUBLIC OF GERMANY MI

DATE MAILED
09/27/90

116213

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,379,083	171	495	----	06/263,719	04/05/83	05/14/81	08	NO	PAID
2	4,379,774	171	495	----	06/303,775	04/12/83	09/21/81	08	NO	PAID
3	4,379,785	171	495	----	06/217,524	04/12/83	12/17/80	08	NO	PAID
4	4,379,900	171	495	----	06/270,489	04/12/83	06/04/81	08	NO	PAID
5	4,381,268	171	495	----	06/283,659	04/26/83	07/15/81	08	NO	PAID

EXHIBIT B-2

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000149

75M7/1007

HOECHST AKTIENGESELLSCHAFT
ZENTRALE PATENTABTEILUNG
GEBAUDE F 821
65926 FRANKFURT AM MAIN
GERMANY TX

DATE MAILED
10/07/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CODE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,379,785	185	2820	----	06/217,524	04/12/83	12/17/80	12	NO	PAID

Patent Maintenance Fees - Public Inquiry

Patent#: 4379785 Filed: 12/17/80 Issued: 04/12/83 Serial#: 06217524
Status: 4th, 8th And 12th Year Fees Paid Sml Entity: NO
Window Opens: Surchg Due: Expiration:
Fee Amt Due:$ Surchg Amt Due:$ Total Amt Due:$
Fee Code: Surchg Code:
Title: HETEROCYCLIC SUBSTITUTED SULFONYL UREAS, AND THEIR USE

Address For Fee Purposes:
HOECHST AKTIENGESELLSCHAFT
ZENTRALE PATENTABTEILUNG
GEBAUDE F 821
65926 FRANKFURT AM MAIN
GERMANY DE

Most Recent Significant Events:
09/20/94 Payment of Maintenance Fee, 12th Year, Large Entity
09/17/90 Payment of Maintenance Fee, 8th Year, PL 96-517
09/15/86 Payment of Maintenance Fee, 4th Year, PL 96-517
Last Event On Maintenance History

END

EXHIBIT C

PAGE 1

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED", A DELAWARE CORPORATION,

WITH AND INTO "HOECHST MARION ROUSSEL, INC." UNDER THE NAME OF "HOECHST MARION ROUSSEL, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE TWENTY-SEVENTH DAY OF DECEMBER, A.D. 1995, AT 11 O'CLOCK A.M.

A CERTIFIED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS FOR RECORDING.

Edward J. Freel, Secretary of State

0613109 8100M

950308409

AUTHENTICATION: 7768416

DATE: 12-27-95

CERTIFICATE OF MERGER

OF

HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED
a Delaware Corporation

WITH AND INTO

HOECHST MARION ROUSSEL, INC.
a Delaware Corporation

PURSUANT TO SECTION 251 OF THE GENERAL CORPORATION LAW OF THE STATE OF DELAWARE

Pursuant to Section 251 of the General Corporation Law of the State of Delaware (the "DGCL"), Hoechst Marion Roussel, Inc., a Delaware corporation (the "Company"), one of the constituent corporations to and the surviving corporation in a merger (the "Merger") with Hoechst-Roussel Pharmaceuticals Incorporated, a Delaware corporation ("HRPI"), has executed this Certificate of Merger in accordance with Section 103 of the DGCL.

The Company hereby certifies that:

1. The names and states of incorporation of the Company and HRPI are:

Name	State of Incorporation
Hoechst Marion Roussel, Inc.	Delaware
Hoechst-Roussel Pharmaceuticals Incorporated	Delaware

2. The Agreement and Plan of Merger dated as of December 18, 1995 (the "Merger Agreement"), by and between the Company and HRPI, has been approved, adopted, certified, executed and acknowledged by each of the Company and HRPI in accordance with Section 251 of the DGCL.

3. The name of the surviving corporation in the Merger is Hoechst Marion Roussel, Inc.

4. The Certificate of Incorporation of the surviving corporation shall be the Certificate of Incorporation of the Company, as in effect immediately prior to the effective date of the Merger (the "Effective Date"), until thereafter amended as provided by law, except that Article Fourth of the Certificate of Incorporation shall be amended as of the Effective Date to read as follows: The total number of shares of stock which the Corporation shall have authority to issue is 1,000 shares of voting common and 1,000 shares of non-voting common and the par value of such shares is $.01 per share, amounting in the aggregate to $20.00.

5. The executed Merger Agreement between the Company and HRPI is on file at the principal place of business of the Company, the address of which is as follows: 10236 Marion Park Drive, Kansas City, Missouri 64137-1405.

6. A copy of the Merger Agreement will be furnished by the Company, on request and without cost, to any stockholder of the Company or HRPI.

7. The Effective Date of the Merger shall be January 1, 1996.

IN WITNESS WHEREOF, this Certificate has been executed in accordance with Section 103 of the DGCL, this 22nd day of December, 1995.

HOECHST MARION ROUSSEL, INC.
a Delaware corporation

By: Fred W. Lyons Jr
Name: Fred W. Lyons, Jr.
Title: Chairman of the Board

ATTEST:

By: Rebecca R. Tilden
Name: Rebecca R. Tilden
Title: Assistant Secretary

Date of Message	TO/FROM	Subject
06/23/88	FDA/HRPI	Original IND - #000.
06/30/88	HRPI/FDA	Acknowledges receipt of IND and assigns IND No. 31,759.
07/21/88	FDA/HRPI	Telecon: R. Tucker/J. Weber to request a meeting to discuss our proposed clinical program. Ms. Weber will get back to us in a few days.
08/10/88	FDA/HRPI	Meeting at FDA to discuss the clinical program is set for 8/30/88 at 1:30 pm.
08/23/88	FDA/HRPI	General Correspondence - #001 Confirmation of 8/30/88 meeting to be held in Conf. Room F at 1:30 pm - Summary of presentation.
08/30/88	HRPI/FDA	FAX: J. DeMartino/John Short re: Minutes of meeting 8/30/88. Purpose: Meeting was requested by Hoechst to present clinical development plan & seek FDA input into program.
09/07/88	HRPI/FDA	Review of 6/23/88 submission completed and study may continue. FDA does have comments and requests for further information.
09/22/88	FDA/HRPI	General Correspondence - Serial No. 002 Minutes of 8/30 meeting w/FDA.
10/07/88	HRPI/FDA	Telecon: Dr. Jordan/D. Bucceri re: Carcinogenicity studies to be done at maximally tolerated dose.
10/13/88	FDA/HRPI	Teleconference: R. Tucker, Drs. Schneider, Spiro, Lassman and Dr. Fleming of FDA to discuss outstanding issues from 8/30 meeting held to present HRPI's US Clinical development plan.
10/19/88	HRPI/FDA	FDA comments on our Minutes of 8/30/88 meeting.
11/07/88	FDA/HRPI	Protocol Amendment - Change in Protocol Information Amendment - Clinical Response to FDA's 9/7/88 & 10/19/88 letters. Amendment to Protocol 101. Ser. #003.
12/07/88	FDA/HRPI	Response to FDA request for informtion (MTD in carcinogenicity study). Serial No. 004.
12/13/88	FDA/HRPI	Response to FDA Request for Information Information Amendment - Chemistry, M/C Serial No. 005

Date of Message	TO/FROM	Subject
12/15/88	HRPI/FDA	Telecon: A. Jordan/D. Bucceri re: carcinogenicity studies with MTD.
12/29/88	HRPI/FDA	Telecon: Dr. Jordan/R. Tucker to request a separate carcinogenicity study at MTD.
01/17/89	FDA/HRPI	General Information - Serial No. 006 (MTD in Ca studies).
01/26/89	HRPI/FDA	Telecon: A. Jordan/D. Bucceri re: our 1/17/89 letter (Ca Studies - MTD).
03/03/89		Upjohn to visit HRPI on March 22 & 23 to review IND & correspondence files.
03/10/89	FDA/HRPI	Protocol Amendment - New Protocol Protocol Amendment - New Investigator Submit C. Wysham, MD (Inv.) to Protocol 202 Serial No. 007
03/15/89	FDA/HRPI	Protocol Amendment - New Investigator Submit Drs. L. Jovanovic, Kilo, Klachko, Kreisberg, Ross, Rosenblatt & Synder to Protocol 202 - Serial No. 008.
03/24/89	FDA/HRPI	Protocol Amendment - New Protocol Protocol Amendment - New Investigator Submit Dr. Doane to Protocol 103 Serial No. 009.
04/10/89	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Crus and Hendler to Protocol 202 Serial No. 010.
05/11/89	FDA/HRPI	Protocol Amendment - New Investigator. Submission Serial No. 011. Submit Drs. Boden Flood, Malone & Selam (Inv.'s) to Protocol 202.
06/09/89	FDA/HRPI	Protocol Amendment - New Protocol (#104). Protocol Amendment - New Investigator. Submit Dr. Herron (Inv.) to Prot. 104. Submit Drs. Browning, Georgopoulos, Holvey, Lodewick & Schade to Prot. 202. Serial #012.
07/13/89	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Gorson to Prot. 202. Serial No. 202.
08/03/89	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Skor, Tung (Inv's) & Dr. Macduff (Co-Inv.) to Prot. 202. Serial No. 015.
09/06/89	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Broadstone, Burks & Schwartz to

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09/06/89	FDA/HRPI	Protocol 202. Serial No. 017.
09/21/89	FDA/HRPI	Annual Progress Report #016.
10/05/89	FDA/HRPI	Information Amendment - Pharmacology. Results of completed ADME studies in animals Serial No. 018.
10/16/89	FDA/HRPI	Information Amendment - Toxicology. Serial No. 019.
10/30/89	FDA/HRPI	Telecon: R. Tucker/J. Weber to set date for tox mtg.(doses for carcinogenicity studies) for 490 & 843.
11/07/89	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Ojile (Co-Investigator) to Prot. 202. Serial No. 020.
11/13/89	HRPI/FDA	Tox meeting scheduled for 12/6 at 10:00 at FDA's Metabolic & Endocrine Division Conf. Room.
12/12/89	FDA/HRPI	Minutes of December 6 tox meeting at FDA.
01/10/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Ruegemer to Protocol 202. Serial NO. 021.
01/10/90	FDA/HRPI	Telecon: R. Tucker/J. Weber to request copy of FDA's minutes of the 12/12 Tox meeting.
01/16/90	HRPI/FDA	FDA's Minutes of Preclinical Tox Meeting held at FDA on 12/6/89.
01/23/90	FDA/HRPI	Information Amendment - Pharm/Tox. Serial No. 022.
03/06/90	FDA/HRPI	Information Amendment - Toxicology. Serial No. 023.
04/20/90	FDA/HRPI	Protocol Amendment - Change in Investigator (Change in Study Site). Protocol Amendment - New Investigator (J. Herron). Protocol Amend New Protocol (105). Serial No. 024.
06/14/90	FDA/HRPI	Protocol Amendment - Change in Study Site. Protocol Amendment - New Investigators (R. Hendler, MD, R. Goldberg, MD, C. Leslie, MD for Protocol 201). Protocol Amendment - New Protocol (201). Serial No. 026.
06/14/90	FDA/HRPI	Information Amendment - Toxicology. Serial No. 025.

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06/14/90	FDA/HRPI	Information Amendment - Toxicology. Serial No. 025.
07/05/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. S. Davis, Kreisberg, M. Davis, Raskin & Rendell to Protocol 201. Serial No. 027.
07/10/90	FDA/HRPI	Information Amendment - Pharmacology. Serial No. 028.
07/17/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Clarke,Georgopoulos, Meenan and Reeves to Protocol 201. Serial No. 029.
07/19/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Tung to Protocol 201; Change of Address for Dr. Snyder under Prot. 202. Serial No. 030.
08/08/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Clark, Kilo, Klachko, Krosnick, Malone & Schwartz to Protocol 201. Serial No. 031.
08/08/90	FDA/HRPI	Information Amendment - Toxicology. Serial No. 032.
08/20/90	HRPI/FDA	Telecon: A. Jordan/R. Tucker re: doses for the rat Ca study.
08/28/90	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 033. Submit Drs. Bansal, Haag, Kolterman & Metzger to Prot. 201.
08/31/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Boden & Jovanovic to Prot. 201. Serial No. 034.
08/31/90	FDA/HRPI	Telecon: D. Bucceri/Dr. A. Jordan re: tox requirements for Rec. Human Insulin.
09/10/90	FDA/HRPI	Annual Progress Report #035.
09/12/90	FDA/HRPI	Telecon: D. Bucceri/Dr. Rhee to respond to Dr. A. Jordan's question about NZ White rabbits used in the teratology study.
09/26/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Holvey to Protocol 201. Serial No. 036.
11/12/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Blonde, Gerich, Knopf & Skor to

Date of Message	TO/FROM	Subject
11/12/90	FDA/HRPI	Protocol 201. Serial No. 037.
11/29/90	FDA/HRPI	Telecon: J. Schneider/Dr. Fleming re: number of patients in qd/bid study, evaluation of efficacy, etc.
11/29/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Karam & Kennedy to Protocol 201. Serial No. 038.
12/27/90	FDA/HRPI	Preclinical IND Safety Report.
12/27/90	FDA/HRPI	Preclinical IND Safety Report. Serial #039.
01/03/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Morrison to Prot. 201. Serial #040.
02/07/91	FDA/HRPI	Information Amendment - Investigator's Brochure; Toxicology. (Submit Investigator's Brochure - Update (edition 12/90) and Four Final Toxicology Reports). Serial No. 041.
02/14/91	FDA/HRPI	Protocol Amendment - New Protocol, New Investigator - (Dr. Raskin to Prot. 301 & Dr. Rosenblatt to new Prot. 205) Serial #042.
03/08/91	FDA/HRPI	Information Amendment - Chemistry, Manufacturing & Controls; Clinical. Serial #043.
03/12/91	FDA/HRPI	Information Amendment - Toxicology. Serial No. 044.
03/22/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators Browning, Mather, Michie, Prendergast, Reynolds, Rosenstock & Snyder to Protocol 205. Serial #045.
04/17/91	FDA/HRPI	Protocol Amendment - New Protocol, New Investigator. Submit Dr. Wicht to new Protocol 106. Serial No. 046.
04/30/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocols 201, 205 & 301Serial No. 047.
05/14/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocols 205 & 301. Serial No. 048.
05/31/91	FDA/HRPI	Information Amendment - C/M/C. Serial #049.
06/04/91	FDA/HRPI	Foreign Case No: 900707T01M.
06/04/91	FDA/HRPI	Foreign Case No: 900510T01M.

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11/29/90	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Karam & Kennedy to Protocol 201. Serial No. 038.
12/27/90	FDA/HRPI	Preclinical IND Safety Report. Serial #039.
01/03/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Morrison to Prot. 201. Serial #040.
02/07/91	FDA/HRPI	Information Amendment - Investigator's Brochure; Toxicology. (Submit Investigator's Brochure - Update (edition 12/90) and Four Final Toxicology Reports). Serial No. 041.
02/14/91	FDA/HRPI	Protocol Amendment - New Protocol, New Investigator - (Dr. Raskin to Prot. 301 & Dr. Rosenblatt to new Prot. 205) Serial #042.
03/08/91	FDA/HRPI	Information Amendment - Chemistry, Manufacturing & Controls; Clinical. Serial #043.
03/12/91	FDA/HRPI	Information Amendment - Toxicology. Serial No. 044.
03/22/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators Browning, Mather, Michie, Prendergast, Reynolds, Rosenstock & Snyder to Protocol 205. Serial #045.
04/17/91	FDA/HRPI	Protocol Amendment - New Protocol, New Investigator. Submit Dr. Wicht to new Protocol 106. Serial No. 046.
04/30/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocols 201, 205 & 301Serial No. 047.
05/14/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocols 205 & 301. Serial No. 048.
05/31/91	FDA/HRPI	Information Amendment - C/M/C. Serial #049.
06/04/91	FDA/HRPI	Foreign Case No: 900707T01M.
06/04/91	FDA/HRPI	Foreign Case No: 900510T01M.
06/04/91	FDA/HRPI	Foreign Case No: 199100595HAG.
06/06/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators J. Lock, MD, J. Mersey, MD and S. Schneider, MD to Protocol 205. Serial

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06/06/91	FDA/HRPI	#050.
06/21/91	FDA/HRPI	Information Amendment: C/M/C. Serial #054.
06/21/91	FDA/HRPI	General Information: Confirmation of July 11 meeting. Serial #055.
06/27/91	HRPI/FDA	FDA meeting originally scheduled for July 11 at 10 am has been rescheduled for 1-3 pm on the same day.
07/09/91	FDA/HRPI	Information Amendment - Toxicology (Request for Meeting). Serial No. 056.
07/19/91	HRPI/FDA	Telecon: Dr. A. Jordan/R. Tucker to inquire as to why we requested a meeting. Meeting is tentatively scheduled for 8/15 at 10 am in Room 14B-04.
07/23/91	FDA/HRPI	Protocol Amendment - New Investigator (J. Doane, MD). Serial No. 057.
07/26/91	FDA/HRPI	Telecon: R. Tucker/Dr. Jordan re: meeting with FDA on toxicology matters. Meeting is confirmed for 8/15 at 10 am in Rm. 14B-04.
07/29/91	FDA/HRPI	Minutes of July 11, 1991 meeting.
08/05/91	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 058.
08/13/91	FDA/HRPI	General Correspondence - Request for Comments (Meeting) re: Protocol 305. Serial No. 060.
08/20/91	FDA/HRPI	Minutes of August 15 Toxicology Meeting at FDA.
08/28/91	FDA/HRPI	General Correspondence - Desk Copies of Submission Serial No. 060 (Protocol 305) to L. Baithwaite.
08/29/91	FDA/HRPI	Foreign Case No. 910487T01M.
09/13/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocol 205 & 301. SErial No. 062.
09/23/91	FDA/HRPI	Annual Progress Report #059.
09/25/91	FDA/HRPI	Protocol Amendment - New Investigator. Protocol 201. Delete Dr. Georgopoulos as principal investigator and replace w/Dr. Saudek. Serial #063.

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09/25/91	HRPI/FDA	FDA's Minutes of 9/1 meeting with HRPI and Upjohn.
10/15/91	FDA/HRPI	General Correspondence - comments on FDA's Minutes of 9/11 meeting. Serial No. 065.
10/24/91	FDA/HRPI	Submt Drs. Levy and Moore to Protocol 205; Dr. Peiris to Protocol 205A; Dr. Hsueh to Protocol 301. Submit Amendment A to Prot. 205.
11/05/91	FDA/HRPI	Information Amendment - C/M/C. Serial #067.
11/06/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit N. Friedman, MD to Protocol 205. Serial No. 068.
11/18/91	FDA/HRPI	Information Amendment - Pharmacology/Toxicology. Serial No. 069.
12/04/91	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Serial No. 071.
12/19/91	FDA/HRPI	Protocol Amendment - New Investigator. Submit A. Bowen, MD., D. Garg, Ph.1D. & D. Weidler, MD to Protocol M/5220/0003. Serial No. 072.
12/23/91	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Serial No. 073.
01/15/92	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Serial No. 074.
01/20/92	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 075.
01/21/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit R. Byyny, MD to Protocol 301. Submit G. Gollapudi, MD to Protocol 205. Serial No. 076.
01/28/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol (P5220-0005). Serial No. 077.
02/07/92	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Submit J. Seibold, MD to Protocol 113. Serial No. 078.
02/21/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol (P-5220-0008). Serial No. 079.
02/21/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol (P-5220-0008) Serial No. 079.

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03/04/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Aronoff, Cyrus, Haag and McGill to Protocol M/5220/001. Serial #080.

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03/04/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Aronoff, Cyrus, Haag and McGill to Protocol M/5220/001. Serial #080.
03/13/92	FDA/HRPI	Protocol Amendment - New Investigator. Add Investigators to Protocols 205 and 301. Serial No. 082.
03/13/92	FDA/HRPI	Protocol Amendment - Change in Protocol. Serial 081.
03/19/92	FDA/HRPI	Protocol amendment - New Investigator. Serial #083.
04/09/92	FDA/HRPI	Foreign Case: Reproduction Toxicity Findings in Rats. Serial #084.
04/13/92	FDA/HRPI	Protocol Amendment - New Investigator; New **Protocol 305. Serial No. 085**
04/20/92	HRPI/FDA	FDA's minutes of our 7/11/91 meeting to discuss clinical development plan. **(Fax from FDA)**
04/20/92	FDA/HRPI	Protocol Amendment: New Investigator - S. Singh, MD and F. Zieve, MD, Ph.D. Serial No. 086.
04/23/92	FDA/HRPI	Protocol Amendment: New Protocol/New Investigator. Inv. J. Doane, MD under new Protocol 112. Serial No. 087.
04/27/92	FDA/HRPI	**Protocol Amendment: New Protocol 0009 - companion to 0001/New Investigator - Serial No. 088.**
05/12/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol. Submit P. Leese, MD to New Protocol 109. Serial #089.
05/13/92	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Submit J. Kisicki, MD to new Protocol P-5220-0010 (US/118). Serial #091.
05/13/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Littlejohn & White to Protocol M/5220/001. Serial #090.
05/21/92	FDA/HRPI	Protocol Amendment - Change in Protocol. Protocol 301, Amendment II). Serial No. 093.
05/21/92	FDA/HRPI	Meeting w/FDA scheduled for 6/9, 2-4 pm in Conference Room I.
05/22/92	FDA/HRPI	General Correspondence - Pre-Meeting subm'n. Serial No. 092. I.

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06/03/92	FDA/HRPI	Information Amendment - Toxicology. Serial No. 094.
06/11/92	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 096.
06/11/92	FDA/HRPI	Protocol Amendment - New Investigator. Inv. D. Bunner & Matlock, MD (Pror. M/5220/0001) & Inv. Azorr, Cyrus, Dills, Freedman, Lucas, Doyle, Podlecki, Ricaurte, MD & J.White, Pharm.D. (M/5220/0009). Serial No. 095.
06/12/92	FDA/HRPI	Protocol Amendment - New Investigator. Inv. Berhanu, Prendergast, Krosnick, MD (Protocol 205) & Cataland, Holvey, Cohen, Tung, MD (Protocol 301) and J. Insel, MD (Prot. 305). Serial No. 097.
06/24/92		Draft agenda for 7/22-23 meeting with HAG and Upjohn.
06/25/92	FDA/HRPI	Minutes of June 9, 1992 meeting at FDA.
06/26/92	HRPI/FDA	Copy of FDA's minutes of 6/9 meeting.
07/09/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol. Submit A. Dietz, Jr., MD to new Protocol P/5220/0006 (US/119--). Serial No. 099.
07/23/92	FDA/HRPI	Protocol Amendment: New Investigator. Serial No. 101.
07/27/92	FDA/HRPI	Information Amendment - Pharmacology. Serial No. 103.
07/28/92	FDA/HRPI	Foreign Case No. 199200923HAG.
07/28/92	FDA/HRPI	Protocol Amendment - New Investigator (P. Conlin & S. Swartz, MD to Prot. 301. Sreial No. 104.
07/29/92	FDA/HRPI	Protocol Amendment - New Investigator - Protocol M/5220/0001. Serial No. 100.
08/12/92	FDA/HRPI	Information Amendment - Toxicology. Serial No. 105.
08/17/92	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 106.
08/17/92	FDA/HRPI	Protocol Amendment - New Investigator/New Protocol. Serial No. 107.

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08/18/92	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 109.
08/24/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit U. IKabadi, MD to Protocol 305. Serial No. 110.
08/26/92	FDA/HRPI	Information Amendment - Toxicology. Serial No. 111.
09/03/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit B. Hoogwerf, MD to Protocol 305. Serial No. 305.
09/22/92	FDA/HRPI	Annual Progress Report #108.
09/24/92	FDA/HRPI	Foreign Case: Reproduction Toxicity Findingsin Rats. **#116.**
09/25/92	FDA/HRPI	Protocol Amendment - New Investigator, New Protocol. Submit R. Dixon, MD to new Protocol M/5220/0013.
09/25/92	FDA/HRPI	Foreign Case Number: 199202279HAG.
10/19/92	FDA/HRPI	Foreign Case Nos. 900707T01M, 910487T01M & 199200595HAG (follow-up safety report). **#118**
10/19/92	FDA/HRPI	Protocol Amendment - New Investigator; New Protocol. Submit R. Henry, MD to New Protocol 207. Serial No. 119.
11/02/92	FDA/HRPI	Protocol Amendment - New Investigator. Submit Drs. Cefalu and Matlock to Protocol M/5220/0009. Submit DRs. Garg & Sonnenberg to Protocol M/5220/0013. Serial No. 122.
11/05/92	FDA/HRPI	Foreign Case: Carcinogenicity Study in Mice. Serial #121.
11/06/92	FDA/HRPI	Protocol Amendment - New Investigators. Submit Investigators to Protocols 108, 203, 205 301, 305. Submit Amendment 1 to Protocol 301. Serial No. 123.

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11/10/92	FDA/HRPI	Amendment to Annual Report dated 9/22/92. Submitting a revised Investigator's Brochure Serial No. 120.
12/30/92	FDA/HRPI	Information Amendment - Clinical: Final Clinical/Statistical Reports. Request for Review & Meeting. Serial No. 124.
01/08/93	FDA/HRPI	Protocol Amendment - New Investigator. Submit Investigators to Protocol M/5220/ 0001. Serial No. 125.
01/13/93	FDA/HRPI	Protocol Amendment - Change in Protocol Submit Amendment A to Protocol 207. Serial No. 126.
01/18/93	HRPI/Upjn	Telecon: R.Tucker/Jan Enzinger (Upjohn - Regulatory) re: Toxicology - should consider holding meeting to discuss carcinogenicity findings.
01/22/93	FDA/HRPI	Foreign Case: Carcinogenicity Study in Mice (follow-up safety report). Serial No. 127.
01/25/93	FDA/HRPI	Protocol Amendment - New Investigator. Protocol Amendment - Change in Protocol (Amendment A to Protocol 203). Serial #128.
01/27/93	FDA/HRPI	Desk copies of final reports & sample data appendices sent to FDA on 12/30/92. Need to obtain comments re: presentation, format & display of data. Meeting scheduled for 2/22/93 from 9:00 - 10:00.
01/29/93	File	FDA Meeting: Clinical/Statistical Reports 201/202 is scheduled for February 22, 1993, 9:00-11:00 at FDA.
02/05/93	FDA/HRPI	Information Amendment - Chemistry, Manufacturing and Controls. Serial No. 129.
02/05/93	FDA/HRPI	Telecon: Dr. Dan Marticello/W-C. Huang/ J. Zimmerman re: 2/22/93 meeting. If useful to discuss statistical questions for Protocol 201 and 202 reports before meeting.
02/23/93	FDA/HRPI	Protocol Amendment - New Investigator. Submit Dr. Vestal to Protocol 205 and Dr. Kayne to Protocol 301. Serial No. 130.
02/25/93	FDA/HRPI	Protocol Amendment - New Investigator. Submit Co-Investigators (J. Fammartino, C. Johnson & A. Nothnagel) to Protocol M/5220/0001. Serial No. 131

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03/04/93	File	Minutes of Meeting with FDA to Discuss Format and Presentation of HOE 490 Clin/Stat Reports, February 22, 1993.
04/23/93	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 132.
04/27/93	FDA/HRPI	Information Amendment - Chemistry, Manufacturing and Controls. Serial No. 133.
05/14/93	FDA/HRPI	General Correspondence - Request for Pre-NDA Meeting. Serial No. 134.
06/04/93	FDA/HRPI	Protocol Amendment - Change in Protocol. Submit Amendment II to Protocol 203B. Serial No. 135.
06/07/93	FDA/HRPI	Information Amendment - Pharmacology/ Toxicology. Serial No. 136.
06/07/93	HRPI/FDA	Telecon: J. DeMartino/John Short re: FDA wanted confirmation that Pharmacology & Chemistry would NOT be discussed at Pre-NDA Mtg. HRPI confirmed that format & content of safety & efficacy summs. only to be discussed
06/09/93	File	Pre-NDA Meeting, 7/7/93 from 1:00 - 3:30 p.m. in Chesapeake Room. Rehearsals on 6/17/93 & 6/18/93. D. Viveash & Frank Ogrinc from TUC will also attend.
06/21/93	FDA/HRPI	Telecon: J. DeMartino/John Short re: 2 hours sufficient for Pre-NDA meeting scheduled for July 7.
06/29/93	FDA/HRPI	General Correspondence - Confirmation of Pre-NDA Meeting. Serial No. 137.
07/21/93	FDA/HRPI	Protocol Amendment - New Investigator. Serial No. 138.
07/21/93	File	Minutes of Pre-NDA Meeting - July 7, 1993.
08/02/93	FDA/HRPI	Information Amendment - Pharmacology/ Toxicology. Serial No. 139.
08/11/93	FDA/HRPI	Copy of 11/5/92 submission. Sent all investigators letter reqsting informed consent be modified. Copy of 6/7/93 Pharm/Tox info amend regarding rat carcinogenicity.
08/11/93	FDA/HRPI	Faxed info to John Short per his request re:

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08/11/93	FDA/HRPI	adenomas in mice study. Dr. Rhee reqstd statement be revised. For Ca studies must give amount of drug in terms of blood levels as opposed to mg/kg.
08/13/93	FDA/HRPI	General Correspondence - Pre-NDA meeting follow-up. Serial No. 140. **- Revised Stat. Analysis.**
08/13/93	FDA/HRPI	Protocol Amendment - Change in Protocol. Amendment II for Protocol 305. Serial No. 141.
08/19/93	FDA/HRPI	Telecon: R. Tucker/A. Schwink/Dr. Jordan re: At Pre-NDA mtg on 7/7/93 focus was clinical. Dr. Fleming suggested contact Dr. Jordan re: preclinical issues of concern. 3 animal tox findings were more of a labeling issue.
08/20/93	FDA/HRPI	Protocol Amendment - New investigator. Serial No. 142.
08/20/93	FDA/HRPI	Protocol Amendment - New investigator. Serial No. 143.
08/23/93	HRPI/FDA	Telecon: R. Tucker/John Short re: submitting BE study 2-3 months after submission of ONDA. If BE stdy not included in ONDA, cannotguarantee that review completed w/in 6 mo. Must send letter to Sobel reqsting answer.
08/24/93	**HRPI/FDA**	**Telecon R. Tucker/A. Schink/Jordan (FDA) Re: Tox Issues & Labeling.**
08/30/93	FDA/HRPI	Information Amendment - Toxicology. Serial No. 144.
09/07/93	HRPI/FDA	Telecon: J. DeMartino/Dr. Marticello re: follow-up to 8/13/93 letter asking to review statistical plan/Protocol 305. Problem with CBG (capillary blood glucose) control. Still "premature statistically".
09/17/93		**Telcon: R. Tucker/J. Short (FDA); Re: Tox Request**
09/20/93	FDA/HRPI	Annual Progress Report #145.
09/28/93	HRPI/FDA	FAX Tucker/John Short re: informal response to request to review revised statistical plan for HOE 490 Protocol 305.
09/30/93	FDA/HRPI	Foreign Report: 199303028HAG. Serial No. 146. IND Safety Report.
10/26/93	HRPI/FDA	FDA refers to 11/5/93 communication (L. Frau) re: preclinical safety report from carcinogenicity study in mice resulting in modification of informed consent. FDA completed review & requests inf. consent be

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10/26/93	HRPI/FDA	further revised.
11/17/93	FDA/HRPI	Telecon: R. Tucker/John Short re: official status of revised statistical plan for Prot. 305 submtd on 8/13/93. Short called back 11/17/93 & stated Dr. Sobel said "fine". No official letter will be sent.
11/23/93	FDA/HRPI	Telecon: J. DeMartino/Dr. Fleming re: preparation of partial draft of his Clinical Review according to outline given us after pre-NDA meeting last July. Outline must be submitted w/NDA & may become a standard request.
11/23/93	FDA/HRPI	General Correspondence - Minutes of Telephone Contact of November 17, 1993. Serial No. 147.
11/30/93	HRPI/FDA	FAX to DeMartino from John Short re: FDA's minutes of 7/7/93 pre-NDA meeting.
12/02/93	FDA/HRPI	Protocol Amendment - New Protocol - 8/USA/110/- Information Amendment - C/M/C. Serial No. 148.
12/10/93	File	File memo attaching copy of FDA's minutes of 7/7/93 Pre-NDA meeting.

DATE	TO/FROM	SUBJECT/ABSTRACT
BOOK 1		
1/3/94	FDA/HRPI	Protocol Amendment - New Investigator. SN 149. Protocol 301.
1/13/94	HRPI/FDA	Telecon: Tucker/Dr. Rhee (reviewing pharmacologist) re: 6/7/93 submission providing diskettes of rat & mouse CA studies. Disk failed. FDA uses AST WordPerfect 5.1 or 6.0. Can HRPI provide that format?
1/19/94	FDA/HRPI	Information Amendment - Toxicology (Rat and Mouse Oncology Studies - Data Diskettes). SN 150.
3/4/94	FDA/HRPI	IND Safety Report, Foreign Case No.: 199303028HAG, Serial No. 151
3/28/95	FDA/HRPI	Submission: Amendment to Annual Progress Report - SN 152
4/5/94	FDA/HRPI	Protocol Amendment - New Protocol SN153. Protocol 120
4/7/94	FDA/HRPI	Protocol Amendment - Change in Protocol - 8/USA/120/-, SN154
6/3/94	FDA/HRPI	FDA Contact Report. Re: 24/mo mouse, 30/mo rat carcinogenicity Studies submitted 6/7/93 doc no. 9619 & 9620. FDA/Dr. Rhee, HRPI/JLD
6/20/94	FDA/HRPI	FDA Contact Report. Phone conversation between Dr. A. Fleming/FDA & JLD/HRPI to discuss NDA ITem 12 - CRF's.
6/23/94	FDA/HRPI	FDA Contact Report. Phone conversation between Central Document Room and JLD/HRPI re: assigning a number for HOE 490 NDA.
6/29/94	FDA/HRPI	FDA Contact. Phone conversation between Helen Hubler/HPRI QA and Gretchen Hahn/FDA re: Drug Listing.
7/6/94	FDA/HRPI	Protocol Amendment - New Protocol-New Investigator 1/USA/121/- SN
7/29/94	FDA/HRPI	FDA Contact Report - Phone conversation between J. Short/FDA & JLD/HRPI to discuss HOE 490 NDA, Glubate Bioequivalence and Diabeta
8/1/94	FDA/HRPI	FDA Contact Report-Phone conversation between JLD, L. Tive & Dr. Alex Fleming to discuss outline for clinical review.
9/1/94	FDA/HRPI	General Correspondence, Submission SN 156
9/13/94	FDA/HRPI	General Correspondence, Submission SN 157. Also sent copy and 3 diskettes to Dr. Fleming.
9/23/94	FDA/HRPI	Annual Progress Report, Serial No. 158.
10/14/94	FDA/HRPI	General Correspondence Submission, Serial No. 159

7/5/95, 7/7/95, 7/11/95	FDA/HRPI	FDA Contact Report - Barry Reit contacted John Short (CSO, Metabolism & Endocrine Durg Products) to discuss the status of responses to the FDA
7/27/95	FDA/HRPI	Submission: Annual Progress Report , Serial No. 160.
10/20/95	FDA/HRPI	Submission: General Correspondence, Serial No. 161. Submitted to both the IND and the NDA. Phase 4 Protocol.

DATE	TO/FROM	SUBJECT/ABSTRACT
BOOK 1		
6/20/94	HRPI	FDA Contact Report. Phone conversation between Central Document Room & JLD/HRPI to assign a number for HOE 490 NDA.
8/1/94	HRPI	FDA Contact Report. Phone conversation between JLD, L. Tive & Dr. Alexander Fleming, group leader to discuss outline for clinical review (the fleming document).
8/26/94	HRPI	FDA Contact Report-Phone conversation bewteen JLD & Heather Pedersen Re: timing of pre-approval inspection.
8/26/94	HRPI	FDA Contact Report-Phone conversation between JLD, W.C. Huang & J. Zimmermann with Dr. Dan Marticello to discuss delivery of SAS data to the biostatistics reviewer.
8/31/94	FDA/HRPI	Submission of HOE490, NDA , original new drug application along with User Fee Cover Sheet.
9/1/94	HRPI/FDA	Confirmation of receipt for submission of NDA, Also a letter from Enid Galliers/FDA to B. Reit notifying us that they are in review of our NDA submission.
9/22/94	HRPI	Fax from B. Reit to A. Chen as requested - responses from previous teleconference
9/22/94	HRPI	FDA Contact Report-Phone conversation between P. Chaikin, B. Reit/HRPI & T. Chen, J. Hunt/FDA to disucss 490 fileability issues.
9/22/94	HRPI	FDA Contact Report- Phone conversation between BR, U. Shukla, D. Voss, J. Schneider, L. Setescak to T. Chen & J. Hunt of FDA for HOE490, fileability issues.
9/23/94	FDA/HRPI	Fax sent to A. Chen; responses todiscuss by previous teleconference with B. Reit, U. Shukla, J. Schneider.
9/26/94	HRPI	FDA Contact Report-Phone conversation between JLD, R.Dix, D. Radzik, L. Setescak, U. Shukla, G. Cunningham & John Hunt, A. Chen/FDA to discuss Follow-up to fax transmitted on 9/23/94.
9/28/94	FDA/HRPI	Fax sent to both Dr. John Gueriguian & Dr. Alexander Fleming re: confirmation of their request re: annotating the Clinical Outline was sent
9/27/94	HRPI	FDA Contact Report-Phone conversation between JLD & John Gueruguian/FDA to discuss Clinical Review of the NDA: Clinical Outline (Fleming Document)

9/27/94	HRPI	FDA Contact Report-Phone conversation between JLD & John Short/FDA to discuss copy of Environmental Assessment section of the C/M/C section of the NDA.
9/29/94	FDA/HRPI	Sent 4 EA section volumes to Dr. Paul Vincent (1.9, 1.10, 1.11, 1.12) orignal date 8-31-94.
10/6/94	HRPI/FDA	Letter from S. Sobel to B. Reit informing us that the intial screening of Item 6 is complete & we must submit in vitro dissolution profiles to them.
10/13/94	HRPI	FDA Contact Report-Phone conversation between JLD & Mr. John Short discussing NDA - Safety update, submitting data during FDAreview.
10/14/94	FDA/HRPI	General Correspondence Submission to S. Sobel "Outline for Clinical Review". Annotation version.
10/20/94	HRPI	FDA Contact Report - Phone conversation between JLD & Dr. Japo Choudhury Re: Statistical Review of the NDA; Original New Drug
11/3/94	HRPI	FDA Contact Report - phone conversation between JLD & John Short discussing NDA Review: October 6, FDA letter Advisory Committee
11/10/94	FDA/HRPI	NDA Amendment - Item 10 - Statistics Diskettes,SAS programs requested by Japo Choudhury but sent official letter to S. Sobel.
11/18/94	FDA/HRPI	Item 10 - Statisitcs , sent letter to J. Choudhury w/ letter only to john short.
12/9/94	FDA/HRPI	General Correspondence - to Mr. John Hunt (text copy only to Mr. John Short) Item 6 Summary 1 Review with diskette in Word Perfect.
12/21/94	FDA/HRPI	General Correspondence -Response to FDA Letter of OCtober 6, 1994
12/29/94	FDA/HRPI	New Drug Application, Item 9- Safety Update
1/3/95	HRPI	FDA Contact Report - JLD & Gurston Turner, Preparation for Auditing
1/6/95	FDA/HRPI	Request for Copies of Information Submitted to the Original NDA
1/6/95	FDA/HRPI	FDA Contact Report - phone conversation between JLD & Dr. Albert Chen/FDA to discuss receipt of response to October 6, 1994 FDA letter
1/10/95	FDA/HRPI	NDA Amendment - Package Insert Revisions
1/17/95	FDA/HRPI	FDA Contact Report -Phone conversation JLD contacted Dr. Xavier Ysern to discuss Inspection: Drug Sustance
1/25/95	FDA/HRPI	FDA Contact Report JLD & Dr. Japo Choudhury to discuss FDA request for additional statistical information for Protocol 8/USA/201

1/25/95	FDA/HRPI	Fax sent to Dr. Japo Choudhury (Biopharm): As per his request - 3 tables from Vol 1.542 (7) for subgroup analyses for age, gender & ethnic group.
1/26/95	FDA/HRPI	FDA Contact Report-phone conversation between JLD, E. Holmgreen, W. Sargent, J. Zimmerman & Dr. Japo Choudhury/FDA to discuss FDA request for additional statisitical information for Protocol 8/USA/201.
1/30/95	FDA/HRPI	FDA Contact Report-phone conversation between J. Zimmerman & Drs. Choudhury, Nevius and Takeuchi/FDA re: FDA request for additional statisitical information for Protocol 8/USA/201
1/30/95	FDA/HRPI	FDA Contact Report -phone conversation between JLD & A. Chen to discuss Request for ASCI files of PK/PD Data.
2/2/95	FDA/HRPI	NDA Amendment - Other Information
2/7/95	FDA/HRPI	FDA Contact Report-phone conversation between JLD & Dr. Herman Rhee to discuss Amaryl NDA Item 5: Rat pancreas pathologist's report.
2/17/95	FDA/HRPI	FDA Contact Report-phone conversation between JLD & Herman Rhee to discuss Mutagenicity Study Doc. No. 012264 (Mouse micronucleus test)
2/21/95	FDA/HRPI	FDA Contact Report-phone conversation between ASCII files of PK/PD data as well as Status of NDA review.
2/21/95	FDA/HRPI	General Correspondence: Item 6 Human Pharmacokinetics and bioavailability section
2/27/95	FDA/HRPI	FAX to Dr. Japo Choudhury, from JLD re: draft tables and figures as per his request on Jan. 25, 1995, for HOE 490 Study 201.
2/28/95	HRPI	FDA Contact Report-phone conversation between JLD & John Short to discuss Status of NDa review
3/1/95	HRPI	FDA Contact Report-phone conversations on March 1,3, and 8. JLD (3/1 & 8), JLD & U. Shukla (3/3), Meeting on 3/7/95 with U. Shukla. All included Dr. Albert Chen and a Follow-up to HRPI's response (12/21) to FDA's request for additional information.
3/8/95	HRPI	FDA Contact Report-phone conversation between JLD & Minnie Baylor-Henry to discuss Amaryl pre-approval promotion piece.
3/10/95	FDA/HRPI	Fax sent to Dr. Japo Choudhury, tables presenting the incidence of deaths in US clinical trials
3/14/95	HRPI	FDA Contact Report-phone conversation between JLD & Dr. Herman Rhee to discuss 30-month rat tox study Doc No. 9620 and 1-year dog tox study Doc No. 8577.

3/14/95	HRPI	FDA Contact Report-phone conversation between JLD, U. Shukla & Dr. Albert Chen to discuss 1. FDA Feedback t our December submission and 2. Clarify Dr. Chen's request for additional plots of time-concentration
3/15/95	HRPI	FDA Contact Report-phone conversation between JLD, U. Shukla and Dr. Albert Chen to discuss presentation of data in Item 6 "pivotal studies".
3/16/95	HRPI	FDA Contact Report-phone conversation between JLD & J. Short to discuss Inspection Process
3/17/95	HRPI	FDA Contact Report-phone conversation between JLD & Albert Chen re: NDA review of Item 6
3/17/95	HRPI	FDA Contact Report-phone conversation between JLD, WC Huan, J. Zimmerman & Dr. Japo Choudhury re: f/u to previous requests for additional info.
3/2/95	HRPI	FDA Contact Report-phone conversation between U. Shukla & A. Chen re: Study USA/206
3/23/95	HRPI	FDA Contact Report-phone conversation between WC Huan, J. Zimmerman & Dr. Japo Choudhury re: discussion of methodology used in Protocol 8/USA/205
3/24/95	HRPI/FDA	FAX received from Dr. Masahiro Takeuchi (Bometrics) to JLD re: Sample dataset format
3/24/95	HRPI	FDA Contact Report- JLD & J. Hunt & A. Chen re: Status of FDA's review of our 12/21/94 submission responding to FDA's request for additional dissolution data from tablets made with drug substance at the extremes of the range for surface area.
3/24/95	HRPI	FDA Contact Report-phone conversation between JLD & A. Chen re: Protocol USA/106/DM: Request for data set
3/24/95	HRPI	FDA Contact Report-phone conversation between JLD, WC Huang, J. Zimmerman & Drs. Choudhury and Takeuchi discussion of longitudinal data analysis for Protocl 201
3/24/95	FDA/HRPI	FAX to Dr. A. Chen from JLD re: response to Dr. Chen's question from a March 12, 1995 telephone contract
3/28/95	FDA/HRPI	General Correspondence: Item 6 - Human pharmacology and
3/30/95	FDA/HRPI	General Correspondence: Item 10 - Statisitical Section
3/31/95	HRPI	FDA Contact Report-phone conversation between JLD & A. Chen re: dissolution data submitted December 12, 1995

DATE	TO/FROM	SUBJECT/ABSTRACT
BOOK 2		
4/3/95	FDA/HRPI	FAX to Dr. A. Chen from JLD re: tables identifying site of manufacture of batches of drug products used in bioequivalence studies reported in
4/4/95	HRPI	FDA Contact Report between JLd & Dr. Albert Chen re: Item 6 - Human Pharmacokinetics and Bioavailability section of the NDA.
4/7/95	FDA/HRPI	Diskettes containing Partial Text of Various Report in Wordperfect 5.0 - Sent to Dr. Chen
4/10/95	FDA/HRPI	Submission: General Correspondence: Item 10 - Statistical Section, Desk Copy to Dr. Japo Choudhury additional information on USA/201, 202, 205 and 305.
4/13/95	FDA/HRPI	Submission: General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability, Desk Copy to Dr. Albert Chen with diskette on Protocol 122.
4/14/95	FDA/HRPI	Copy of article entitiled "A Note on Shirley's Nonparametric Test for Comparing Several Dose Levels with a Zero-Dose Control".
4/18/95	HRPI	FDA Contact Report between JLD & Albert Chen re: Request for infomation: Inter-and intra-day variation; Statistical output for Standard
4/19/95	FDA/HRPI	Submission: General Correspondence: Item 6 - Human Pharmacokinetics and Bioavailability, Desk Copy to Dr. Albert Chen with diskettes on demographic data and plasma urine concentrations for many studies:
4/19/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: NDA Draft Statistical Output for Study
4/19/95	FDA/HRPI	Submission Gen. Corr - Item 6 Human PK & Bioavail, Copy Faxed to Dr. Albert Chen for output for Study 124, mean values of pharmacokinetic parameters
4/20/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: information requested concerning content uniformity, isolation & characterization of human metabolic
4/21/95	FDA/HRPI	Submission: General Correspondence: Item 10 - Statistical Section, Desk Copy to Dr. Masahiro Takeuchi re: datasets, approaches and correlation structures.
4/21/95	FDA/HRPI	Submissio: Gen. Corr - Item 6 -Human PK & Bioavail., page replacement for Vol. 85, page 34 entitled " Serum Concentration of M1".
4/21/95	FDA/HRPI	Submission: Gen. Corr - Item 10 - Statistical, Desk Copy to Dr. Japo Choudhury a description of pseudohomogeneity statistic & numeric example used in Protocol 205

4/21/95	HRPI	FDA Contact Report JLD & John Short re: Status of NDA review
4/25/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: sample pages displaying interday variation data for Studies USA/121 and 120.
4/25/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: official submission re: analysis of young vs. elderly Study USA/206
4/25/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: pharmacokinteics table for inclusion in the
4/25/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: recommendations for the section RACE of the PI
4/26/95	FDA/HRPI	Submission Gen. Corr - Item 6 Human PK and Bioavail, Protocol 8/USA/206 - Additional Information, Desk Copy to Dr. Albert Chen
5/1/95	HRPI	FDA Contact Report JLD & Albert Chen 1. 1/A/122 Interday variation and 2. USA/103 Statistical Data
5/3/95	HRPI	FDA Contact Report JLD & Dr. X. Ysern and Mr John Short re: CMC issues and FDA meeting to discuss labeling
5/5/95	HRPI	FDA Contact Report JLD & Dr. Japo Choudhury re: Request for copies of pages and clarification of analysis of Study 305
5/9/95	FDA/HRPI	Submission Protocol Amendment - Change in Sub-investigator
5/9/95	FDA/HRPI	Submission Gen Corr - Item 3 CMC, submitting of revised pages to correct typographical errors in the dissolution specs.
5/9/95	HRPI	FDA Contact Report JLD & John Short re: FDA's review of the package
5/11/95	FDA/HRPI	At the request of Dr. Japo Choudhury, sent copies of figures, tables and pages identified. Not resubmitting this to the NDA.
5/11/95	HRPI	FDA Contact Report - JLD & Dr. Albert Chen discussing various issues
5/17/95	HRPI/FDA	Official Letter re: Pharm & Tox and Chemistry reviews are completed. 4 Comments are included
5/18/95	FDA/HRPI	FAX sent to Dr. Albert Chen re: pages from NDA regarding comparative metabolism, Item 5C, ADME
5/19/95	FDA/HRPI	Submission Gen Corr. - Item 5C nonclinical Pharm & Tox, Desk Copy to Dr. Albert Chen

5/23/95	FDA/HRPI	Submission Gen Corr - Item 6 Human PK and Bioavail, Desk Copy to Dr. Albert Chen re: Summary of PK results, Population Studies, Glimepiride Assay
5/24/95	HRPI	FDA Contact Report JLD & Dr. Albert Chen re: PK section of labeling
5/26/95	HRPI	FDA Contact Report JLD & John Short re: additional time for FDA meeting and Ongoing NDA review
5/26/95	HRPI	FDA Contact Report JLD & Dr. Albert Chen re: request for conference call re: PD/PK data
5/30/95	HRPI	FDA Contact Report JLD & Dr. Albert Chen re: Dissolution Data
5/31/95	FDA/HRPI	Submission Gen Corr: request of Dr. Japo Choudhury aditional pages which were excluded from original request sent (May 11)
5/31/95	HRPI/FDA	Official Letter to BR from S. Sobel, completed review of environmental assessment section of submission and identified deficiencies:
5/31/95	HRPI	FDA Contact Report JLD, L. Setescak & Dr. Ysern (reviewing chemist) re: clarification of May 17 letter starting materials and revised labels
6/1/95	HRPI	FDA Contact Report JLD, R. Dix, D. Radzik, L. Setescak, U. Shukla and J. Hunt & A.Chen re: PK/PD relationship, Reformatted PK section of PI, Hepatic impairment, Excretion of metabolites, USA 206 PD analysis & Formulation information list
6/2/95	FDA/HRPI	Submission Gen. Corr. Item 6 - Human PK and Bioavail, Desk Copy to Dr. Albert Chen re: follow-up to June 1, 1995 teleconference with Mr John Hunt and Dr. Albert Chen
6/2/95	HRPI	FDA Contact Report JLD & John Short re: 1. May 31st letter EA deficiencies and 2. PI
6/5/95	FDA/HRPI	As the request of John Short, a package containing diskette of package insert matching hard copy of the labeling submitted Jan. 10, 1995 in Word Perfect .
6/7/95	HRPI/FDA	Official Letter FAXED to JLD from John Short , upon FDA's completetion of their review of NDA, they have the following comments:
6/7/95	HRPI/FDA	Submission: Gen. Corr. Item 6 - Human PK and Bioavailability Protocol 8/USA/206 Additional Information. Desk Copy to Albert Chen
6/8/95	HRPI/FDA	Telefax from Mr. John Short to Jim DeMartino, 40 pages of revisions for the PI section submitted Jan 10.

6/12/95	FDA/HRPI	Submission: Gen. Corr. Item 6 - Human PK and Bioavailability. Desk Copy to Albert Chen
6/12/95	FDA/HRPI	FAX to Albert Chen from JLD re: preclinical ADME report "determination of protein binding of MEtabolites M1 and M2 of HOE 490".
6/13/95	FDA/HRPI	FAX to Dr. A. Fleming and Dr. J. Gueriguian from JLD thanking them for teleconference and to clarify some PI questions
6/14/95	HRPI	FDA Contact Report - JLD & Dr. Xavier Ysern re: revised labeling requested in May 17 letter from FDA
6/15/95	FDA/HRPI	Submission: Gen. Corr. Item 6 - Human PK and Bioavailability - batch sizes and content uniformity data for Study 121. Desk Copy faxed to Dr. Chen and Mr. Short
6/19/95	HRPI	FDA Contact Report - JLD, W.C. Huang, W. Stager & Dr. Japo Choudhury re: analysis of deaths
6/20/95	FDA/HRPI	Submission: Gen. Corr. Revised Package Insert. Desk Copy faxed to Mr. Short
6/21/95	FDA/HRPI	FAX to Mr. John Short re: FYI that we are overnighting the official submission of the revised package insert & its four parts
6/21/95	HRPI	FDA Contact Report - JLD & Albert Chen re: dissolution and specific surface area and additional labeling changes
6/22/95	FDA/HRPI	Submission: Gen. Corr. Item 3 - CMC Section A.4.b - Methods Validation Data section of Section A - Drug Substance. Desk copy to Albert Chen
6/22/95	FDA/HRPI	FAX to Dr. Japo Choudhury confirming there were no placebo controlled studies in Europe.
6/23/95	HRPI	FDA Contact Report for Meeting with FDA (A. Chen, J. Choudhury, A. Fleming, A. Reb, H. Rhee, J. Short, G. Troendle), HRPI/HAG (Chaikin, Delsile, DeMartino, Draeger, Gau, Huang, Reit, Schneider, Shukla, Zimmerman) to discuss the Package Insert
6/26/95	FDA/HRPI	Submission: Gen. Corr. Response to May 17th 1995 FDA letter
7/5/95	HRPI	FDA Contact Report - B. Reit and John Short to discuss status of responses to FDA.
7/10/95	FDA/HRPI	Submission: Gen. Corr. Response to May 31, 1995 FDA letter concerning the Environmental Assessment section of the NDA.
7/12/95	FDA/HRPI	Submission: Gen. Corr. Labels - Response to May 17th FDA letter. Desk copy to Dr. Ysern

7/12/95	FDA/HRPI	Letter to Dr. Ysern from JLD with attached copy of official submission regarding the draft labels modified to comply with request for word replacement of the word tablets with established name
7/12/95	HRPI/FDA	Official letter from S. Sobel to Dr. Reit re: completed review of NDA with few deficiencies re: hepatic impairment, enzymes, etc.
7/12/95	HRPI/FDA	Official Letter from S. Sobel to Dr. Reit re: our amendment dated June 20 providing for revision in the PI and their comments
7/14/95	HRPI	FDA Contact Report JLD, B. Reit and John Short re: Amaryl NDa review
7/17/95	FDA/HRPI	Submission: Gen. Corr. Item 3 - CMC Updated Stability Data, Drug Substance and Drug Product. Desk copy to Dr. Xavier Ysern
7/19/95	HRPI/FDA	Official Letter from S. Sobel to B. Reit re: acknowledging receipt of July 10 amendment and Due date for User Fee due date is now November 28. Also re: agreement to conduct a Phase 4 study.
7/20/95	FDA/HRPI	Submission: General Correspondence: responses referring to deficiencies stated in FDA letters both dated July 12, 1995
7/27/95	HRPI	FDA Contact Report - JLD & John Short re: outstanding Amaryl issues
7/27/95	FDA/HRPI	FDA Contact Report - JLD & John Short, re: Follow-up to fax transmission, Status of Biopharm review, Gluctrol XL insulin use.
8/2/95	HRPI	FDA Contact Report - JLD & Dr. John Gueriguian & Dr Bruce Stadel to discuss Phase 4 Study
8/4/95	HRPI	FDA Contact Report - JLD & Dr. Xavier Ysern (reviewing Chemist) to discuss labels and starting materials
8/9/95	FDA/HRPI	Submission: Response to July 19, 1995 FDA letter
8/10/95	FDA/HRPI	Submission: General Correspondence: Glucose Meter Data Listing. Desk Copy to Dr. Alex Fleming
8/15/95	HRPI	FDA Contact Report - JLD & Dr. Gurston Turner to discuss request for copies of CRFs line listings and protocols
8/15/95	FDA/HRPI	Submission: General Correspondence: Protocol 305 - Patients with the Adverse Event Symtomic Hypoglycemia. Desk Copy to Dr. Alex Fleming
8/16/95	FDA/HRPI	FAX sent to Dr. John Short from JLD re: Request for teleconfernce to discuss Phase 4 study post-marketing study proposed in FDA leter July 19,

8/17/95	FDA/HRPI	Submission: General Correspondence: Protocols 201 and 205 - Request for copies Sent directly to Dr. Gurston Turner
8/17/95	FDA/HRPI	Submission: General Correspondence: Protocol 8/USA/201 and 205 CRFs. Desk Copy to Dr. Turner
8/21/95	FDA/HRPI	FAX : to Dr. Gurston Turner from JLD re: request for full addresses of the 5 investigators listed in Protocol 201 and 205.
8/28/95	HRPI	FDA Contact Report - JLD & Dr. Wenjen Chen (Biostatistics) re: carcinogenicity data submitted on disks.
8/28/95	FDA/HRPI	Submission: General correspondence: Response to FDA letter dated July 12, 1995 - Biopharmacutics Review Comments Desk Copy to Dr. Chen and Dr. Ysern
8/29/95	HRPI	FDA Contact Report - JLD, J. Schneider, P. Chaikin, H. Stanbrook, C. Canabarro, FDA: S. Sobel, A. Fleming, J. Gueriguian, E. Nevis, J. Short teleconference
8/29/95	FDA/HRPI	FAX - JLD to Mr. John Short, CSO re: NDA 20-496, Amaryl Tablets: Phase 4 Study
8/30/95	HRPI/FDA	Official Letter from S. Sobel to B. Reit re: deficiencies with regards to the EA Section of the amendment submitted on July 10, 1995.
9/7/95	HRPI	FDA Contact Report - JLD & Mr. John Short re: Phase 4 commitment, Acrabose approval, Amaryl action letter and FDA letter expected: re: starting materials
9/11/95	FDA/HRPI	Submission: Safety Update 9/95
9/13/95	HRPI/FDA	Official Letter from S. Sobel to B. Reit re: EA section and starting materials
9/13/95	FDA/HRPI	Submission: Reply to FDA letters of August 30, 1995 (EA) and September 13, 1995 (Starting materials). Desk Copy to Mr. John Short
9/13/95	HRPI	FDA Contact Report D. Bergstrom, D. Radzik, M. Schroeder, L. Setescak & Dr. Albert Chen to discuss questions and responses
9/18/95	HRPI	FDA Contact Report D. Bergstrom, D. Radzik, L. Setescak, U. Shukla, M. Schroeder, & Dr. Albert Chen, questions & answers
9/18/95	HRPI	FDA Contact Report M. Schoeder, Mr. John Short, Amaryl NDA Review Status
9/21/95	HRPI	FDA Contact Report D. Bergstrom, D. Radzik, B. Reit, M. Schroeder, X. Sha, L. Setescak & Dr. Albert Chen

9/25/95	HRPI	FDA Contact Report JLD & J. Pandolfino and Nancy Sager (Office of Chemistry) re: EA Assessment September 13, 1995 submission
9/25/95	FDA/HRPI	Submission: General Correspondence: Response to FDA letter dated August 30, 1995 and September 13, 1995. Faxed desk copy to N. Sager (FDA)
9/28/95	HRPI	FDA Contact Report JLD & Alexander Fleming (Group Leader), re: Package Insert
9/29/95	HRPI/FDA	Official Letter from S. Sobel to B. Reit re: respone to August 28, 1995 amendment addressing biopharmaceutics issues
9/29/95	HRPI/FDA	FAX from John Short (A. Fleming) to JLD with suggested PI revisions for submission dated June 20, 1995
10/4/95	HRPI	FDA Contact Report - JLD & John Short, CSO to discuss status of NDA review
10/5/95	FDA/HRPI	Submission: General Correspondence: Reply to September 29, 1995 FDA Letter. Desk Copy to A. Fleming
10/5/95	FDA/HRPI	FAX sent to Dr. Alexander Fleming from JLD with our responses to FDA suggested revisions on the Amaryl PI.
10/6/95	FDA/HPRI	Submission General Correspondence: Draft Labeling. Desk Copy to Dr. A. Fleming
10/6/95	HRPI	FDA Contact Report - JLD, J. Schneider, P. Chaikin, B.Reit, FDA: Dr. A. Fleming to discuss FDA Comments on June 20 edition of PI
10/9/95	FDA/HRPI	Letter: Amendment: Revision to labeling per September 13, 1995 FDA letter - Page Replacement to October 6, 1995 amendment (Revised Labeling). Desk Copy to Dr. A. Fleming
10/13/95	FDA/HRPI	FAX sent to Mr. John Short from JLD with E. Hamberg's address
10/16/95	FDA/HRPI	Submission: Amendment to Pending Application: Draft Labeling
10/16/95	FDA/HRPI	FAX sent to Mr. John Short from JLD with attached 10/16/95 submission - sent overnight
10/18/95	FDA/HRPI	FAX sent to Mr. John Short from JLD with various cover sheets which John requested to view for his own use
10/20/95	FDA/HRPI	Submission: General Correspondence: Serial No. 161 for both the IND and the NDA - Phase 4 Protocol

10/20/95	FDA/HRPI	FAX sent to Mr. John Short from JLD with the attached 10/20/95 submission - Phase 4 Protocol
10/31/95	HRPI	FDA Contact Report - JLD & John Short to discuss the status of the NDA review and Phase 4 Protocol
10/31/95	HRPI/FDA	Official Letter from Dr. S. Sobel to B. Reit explaining that FDA extended the user fee clock, based on a major amendment received within 3 months of the original user fee date to 11/28/95. This date was incorrectly calculated, it should be 11/30/95.
11/28/95	HRPI	FDA Contact Report - JLD & John Short to discuss Phase 4 Study
11/29/95	HRPI/FDA	FAX from John Short to JLD with revisions of the Amaryl PI after meeting with Dr. Bilstad
11/29/95	FDA/HRPI	FAX to John Short from JLD with some corrections, changes which were requested to further along the PI approval process
11/30/95	FDA/HRPI	FAX sent to J. Short from JLD with the attached Final Draft Package Insert submission which will be submitted officially upon receipt of approval
11/30/95	HRPI/FDA	Official New Drug Application Approvable Letter from J. Bilstad to B. Reit acknowleding and accepting Amaryl for distribution.
11/30/95	FDA/HRPI	Submission: Amendment to Pending Application: Final Draft Labeling

EXHIBIT D-3

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT ORIGINAL EXPIRATION DATE

1. ENTER THE NUMBER OF DAYS FOR THE TESTING PHASE AS DEFINED IN 37 CFR 1.775(c)(1)	2224	
2. ENTER THE NUMBER OF DAYS FOR THE APPROVAL PHASE AS DEFINED IN 37 CFR 1.775(c)(2)	457	
3. ADD LINE 1 AND LINE 2 AND ENTER THE TOTAL HERE		2681
4. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
5. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d)(1)(ii)	0	
6. ADD LINE 4 AND LINE 5 AND ENTER THE TOTAL HERE		0
7. SUBTRACT LINE 6 FRONE LINE 3 AND ENTER THE DIFFERENCE HERE		2681
8. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
9. ENTER THE NUMBER OF DAYS OF THE PREIOD OF LINE 1 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775 (d)(1)(ii)	0	
10. ADD LINE 8 AND LINE 9 AND ENTER THE TOTAL HERE		0
11. SUBTRACT LINE 10 FROM LINE 7 AND ENTER THE DIFFERENCE HERE		2681
12. ENTER THE NUMBER OF DAYS FROM LINE 1	2224	
13. ENTER THE NUMBER OF DAYS FROM LINE 10	0	
14. SUBTRACT LINE 13 FROM LINE 12 AND ENTER THE DIFFERENCE HERE	2224	
15. MULTIPLY LINE 14 BY 0.5 (ONE HALF) AND ENTER THE AMOUNT HERE		1112
16. SUBTRACT LINE 15 FROM LINE 11 AND ENTER THE DIFFERENCE HERE		1569
17. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT	APRIL 12, 2000	
18. ENTER THE EXPIRATION DATE OF PATENT IS EXTENDED BY THE NUMBER OF DAYS ON LINE 16	JULY 19, 2004	
19. ENTER THE DATE OF THE FDA (FOOD AND DRUG ADMINISTRATION) FINAL APPROVAL	NOVEMBER 30, 1995	
20. LIMITATION SET FORTH IN 37 CFR 1.775 (d)(3)	14 YEARS	
21. ADD THE NUMBBER OF YEARS ON LINE 20 TO THE DATE ON LINE 19 AND ENTER THE REVISED DATE HERE	NOVEMBER 30, 2009	
22. ENTER THE EARLIER DATE APPEARING ON LINE 18 OR LINE 21		JULY 19, 2004
23. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)	APRIL 12, 2000	
24. CHECK ONE OF THE FOLLOWING THREE BOXES AND ENTER THE REVISED TIME PERIOD HERE		

		THE PATENT ISSUED AFTER 09/24/84	5 YEARS
	X	THE PATENT ISSUED PRIOR TO 09/24/84 AND NO REQUEST FOR EXEMPTION AS DEFINED IN 37 CFR 1.775(d)(6)(i) WAS FILED PRIOR TO 09/24/84	5 YEARS
		THE PATENT ISSUED PRIOR TO 09/23/84 AND AN EXEMPTION AS DEFINED IN 37 CFR 1.775 (d)(6)(ii) WAS FILED PRIOR TO 09/24/84	2 YEARS

25. ADD THE NUMBER OF YEARS ON LINE 24 TO THE DATE ON LINE 23 AND ENTER THE REVISED DATE HERE	APRIL 12,2005	
26. ENTER THE EARLIER DATE APPEARING ON LINE 22 OR LINE 25		JULY 19, 2004
27. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)		APRIL 12, 2000
28. ENTER THE NUMBER OF DAYS BY WHICH LINE 26 AND LINE 27 DIFFER HERE THIS IS THE LENGTH OF PATENT TERM EXTENSION		1569

EXHIBIT D-4

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT URAA EXPIRATION DATE

1. ENTER THE NUMBER OF DAYS FOR THE TESTING PHASE AS DEFINED IN 37 CFR 1.775(c)(1)	2224	
2. ENTER THE NUMBER OF DAYS FOR THE APPROVAL PHASE AS DEFINED IN 37 CFR 1.775(c)(2)	457	
3. ADD LINE 1 AND LINE 2 AND ENTER THE TOTAL HERE		2681
4. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
5. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d)(1)(II)	0	
6. ADD LINE 4 AND LINE 5 AND ENTER THE TOTAL HERE		0
7. SUBTRACT LINE 6 FRONE LINE 3 AND ENTER THE DIFFERENCE HERE		2681
8. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
9. ENTER THE NUMBER OF DAYS OF THE PREIOD OF LINE 1 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775 (d)(1)(II)	0	
10. ADD LINE 8 AND LINE 9 AND ENTER THE TOTAL HERE		0
11. SUBTRACT LINE 10 FROM LINE 7 AND ENTER THE DIFFERENCE HERE		2681
12. ENTER THE NUMBER OF DAYS FROM LINE 1	2224	
13. ENTER THE NUMBER OF DAYS FROM LINE 10	0	
14. SUBTRACT LINE 13 FROM LINE 12 AND ENTER THE DIFFERENCE HERE	2224	
15. MULTIPLY LINE 14 BY 0.5 (ONE HALF) AND ENTER THE AMOUNT HERE		1112
16. SUBTRACT LINE 15 FROM LINE 11 AND ENTER THE DIFFERENCE HERE		1569
17. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT	DECEMBER 17, 2000	
18. ENTER THE EXPIRATION DATE OF PATENT IS EXTENDED BY THE NUMBER OF DAYS ON LINE 16	APRIL 4, 2005	
19. ENTER THE DATE OF THE FDA (FOOD AND DRUG ADMINISTRATION) FINAL APPROVAL	NOVEMBER 30, 1995	
20. LIMITATION SET FORTH IN 37 CFR 1.775 (d)(3)	14 YEARS	
21. ADD THE NUMBBER OF YEARS ON LINE 20 TO THE DATE ON LINE 19 AND ENTER THE REVISED DATE HERE	NOVEMBER 30, 2009	
22. ENTER THE EARLIER DATE APPEARING ON LINE 18 OR LINE 21		APRIL 4, 2005
23. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)	DECEMBER 17, 2000	
24. CHECK ONE OF THE FOLLOWING THREE BOXES AND ENTER THE REVISED TIME PERIOD HERE		

		THE PATENT ISSUED AFTER 09/24/84	5 YEARS
	X	THE PATENT ISSUED PRIOR TO 09/24/84 AND NO REQUEST FOR EXEMPTION AS DEFINED IN 37 CFR 1.775(d)(6)(I) WAS FILED PRIOR TO 09/24/84	5 YEARS
		THE PATENT ISSUED PRIOR TO 09/23/84 AND AN EXEMPTION AS DEFINED IN 37 CFR 1.775 (d)(6)(II) WAS FILED PRIOR TO 09/24/84	2 YEARS

25. ADD THE NUMBER OF YEARS ON LINE 24 TO THE DATE ON LINE 23 AND ENTER THE REVISED DATE HERE	DECEMBER 17, 2005	
26. ENTER THE EARLIER DATE APPEARING ON LINE 22 OR LINE 25		APRIL 4, 2005
27. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)		DECEMBER 17, 2000
28. ENTER THE NUMBER OF DAYS BY WHICH LINE 26 AND LINE 27 DIFFER HERE THIS IS THE LENGTH OF PATENT TERM EXTENSION		1569

United States Patent [19]

Weyer et al. Glymepiride . HOE 490

[11] **4,379,785**

[45] **Apr. 12, 1983**

[54] HETEROCYCLIC SUBSTITUTED SULFONYL UREAS, AND THEIR USE

[75] Inventors: **Rudi Weyer**, Kelkheim; **Volker Hitzel**, Hofheim am Taunus; **Karl Geisen**, Frankfurt am Main; **Günter Regitz**, Bad Soden am Taunus, all of Fed. Rep. of Germany

[73] Assignee: **Hoechst Aktiengesellschaft**, Frankfurt am Main, Fed. Rep. of Germany

[21] Appl. No.: **217,524**

[22] Filed: **Dec. 17, 1980**

[30] **Foreign Application Priority Data**

Dec. 19, 1979 [DE] Fed. Rep. of Germany 2951135

[51] **Int. Cl.**³ **A61K 31/40**; A61K 31/44; C07D 207/38; C07D 209/46

[52] U.S. Cl. ..... **424/244**; 260/239.3 R; 260/239.3 B; 424/258; 424/263; 424/267; 434/274; 546/141; 546/156; 546/203; 546/205; 546/206; 546/221; 546/243; 546/292; 548/512; 548/528; 548/538

[58] Field of Search ..... 260/326.23, 325 PH, 260/325 R, 239.3 R, 239.3 B, 564/40, 41; 546/203, 205, 141, 11 E, 221, 206, 292, 243, 156; 424/244, 274, 263, 267, 258

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,336,322	8/1967	Weber et al	546/226
3,510,496	5/1970	Aumuller et al.	260/325 PH
3,646,009	2/1972	Winter et al.	564/41
3,655,756	4/1972	Weber et al.	564/41
3,819,633	6/1974	Ambrogi et al.	546/146
3,962,244	6/1976	Weyer et al.	260/256.5 R
4,282,239	8/1981	Weyer et al.	424/274

FOREIGN PATENT DOCUMENTS

1670700	3/1970	Fed. Rep. of Germany .
2103118	8/1972	Fed. Rep. of Germany .
2085759	3/1971	France .

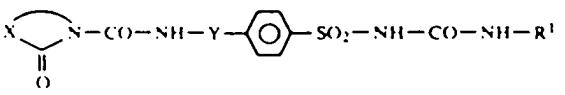
OTHER PUBLICATIONS

79102066.2, European Patent Application Published Jan. 1, 1980 (=AD).

Primary Examiner—Alton D. Rollins
Attorney, Agent, or Firm—Curtis, Morris & Safford

[57] **ABSTRACT**

What are disclosed are sulfonyl ureas of the formula



in which R^1, X and Y are as defined in the specification, and their physiologically acceptable salts, pharmaceutical formulations on the basis of these compounds, and their use in the treatment of diabetes.

6 Claims, No Drawings

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TERM EXTENSION	:	AMARYL
In re Patent of	:	Weyer et al.
Patent No.	:	4,379,785
Issued	:	April 12, 1983
For	:	Heterocyclic Substituted Sulfonyl Ureas, and their Use

AMENDMENT TO APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC §156

February 29, 1996

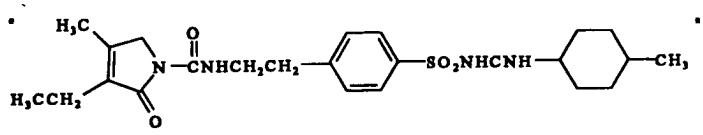
Honorable Commissioner of
Patents and Trademarks
Box Patent Term Extension
Washington, D.C. 20231

Attention: Karen Tyson

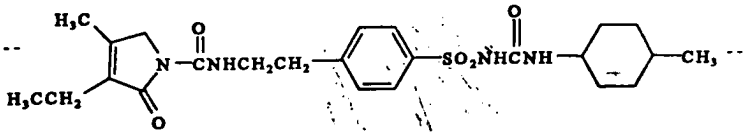
Sir:

Subsequent to filing an application for extension of patent term of U.S. Patent No. #4,379,785 on January 22, 1996, applicants have discovered an inadvertent error in the complete identification of the approved product. Kindly amend the application as follows:

Page 1, line 24, delete



and insert



REMARKS

Entry of this correction is respectfully requested. The "=O" was inadvertently omitted from the drawing of the urea portion of the molecule.

Respectfully Submitted,

Barbara V. Maurer
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